STN - STRUCTURE SEARCH 8-29-04

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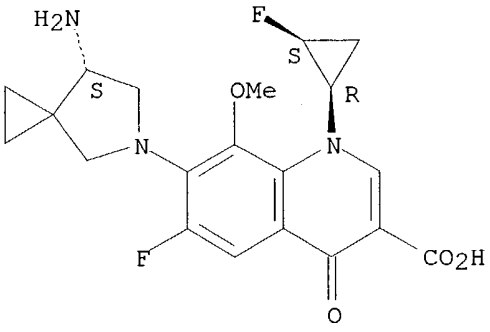
L4 ANSWER 1 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:949480 CAPLUS
DOCUMENT NUMBER: 140:125105
TITLE: Antipneumococcal activity of DK-507k, a New Quinolone, compared with the activities of 10 other agents
AUTHOR(S): Browne, Frederick A.; Bozdogan, Buelent; Clark, Catherine; Kelly, Linda M.; Ednie, Lois; Kosowska, Klaudia; Dewasse, Bonifacio; Jacobs, Michael R.; Appelbaum, Peter C.
CORPORATE SOURCE: Department of Medicine, Hershey Medical Center, Hershey, PA, 17033, USA
SOURCE: Antimicrobial Agents and Chemotherapy (2003), 47(12), 3815-3824
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Agar dilution MIC determination was used to compare the activity of DK-507k with those of ciprofloxacin, levofloxacin, gatifloxacin, moxifloxacin, sitafloxacin, amoxicillin, cefuroxime, erythromycin, azithromycin, and clarithromycin against 113 penicillin-susceptible, 81 penicillin-intermediate, and 67 penicillin-resistant pneumococci (all quinolone susceptible). DK-507k and sitafloxacin had the lowest MICs of all quinolones against quinolone-susceptible strains (MIC at which 50% of isolates were inhibited [MIC50] and MIC90 of both, 0.06 and 0.125 μg/mL, resp.), followed by moxifloxacin, gatifloxacin, levofloxacin, and ciprofloxacin. MICs of β-lactams and macrolides rose with those of penicillin G. Against 26 quinolone-resistant pneumococci with known resistance mechanisms, DK-507k and sitafloxacin were also the most active quinolones (MICs, 0.125 to 1.0 μg/mL), followed by moxifloxacin, gatifloxacin, levofloxacin, and ciprofloxacin. Mutations in quinolone resistance-determining regions of quinolone-resistant strains were in the usual regions of the parC and gyrA genes. Time-kill testing showed that both DK-507k and sitafloxacin were bactericidal against all 12 quinolone-susceptible and -resistant strains tested at twice the MIC at 24 h. Serial broth passages in subinhibitory concns. of 10 strains for a min. of 14 days showed that development of resistant mutants (fourfold or greater increase in the original MIC) occurred most rapidly for ciprofloxacin, followed by moxifloxacin, DK-507k, gatifloxacin, sitafloxacin, and levofloxacin. All parent strains demonstrated a fourfold or greater increase in initial MIC in <50 days. MICs of DK-507k against resistant mutants were lowest, followed by those of sitafloxacin, moxifloxacin, gatifloxacin, ciprofloxacin, and levofloxacin. Four strains were subcultured in subinhibitory concns. of each drug for 50 days: MICs of DK-507k against resistant mutants were lowest, followed by those of sitafloxacin, moxifloxacin, gatifloxacin, levofloxacin, and ciprofloxacin. Exposure to DK-507k and sitafloxacin resulted in mutations, mostly in gyrA.
IT **364069-14-7**, DK-507k
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antipneumococcal activity of DK-507k, New Quinolone, compared with activities of 10 other agents)
RN 364069-14-7 CAPLUS
CN 3-Quinolinecarboxylic acid, 7-[(7S)-7-amino-5-azaspiro[2.4]hept-5-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:949468 CAPLUS
DOCUMENT NUMBER: 140:156809
TITLE: In vitro and in vivo antibacterial activities of DK-507k, a novel fluoroquinolone
AUTHOR(S): Otani, Tsuyoshi; Tanaka, Mayumi; Ito, Emi; Kurosaka, Yuichi; Murakami, Yoichi; Onodera, Kiyomi; Akasaka, Takaaki; Sato, Kenichi
CORPORATE SOURCE: New Product Research Laboratories I, Daiichi Pharmaceutical Co. Ltd., Tokyo, Japan
SOURCE: Antimicrobial Agents and Chemotherapy (2003), 47(12), 3750-3759
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The antibacterial activities of DK-507k, a novel quinolone, were compared with those of other quinolones: ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, sitafloxacin, and garenoxacin (BMS284756). DK-507k was as active as sitafloxacin and was as active as or up to eightfold more active than gatifloxacin, moxifloxacin, and garenoxacin against Streptococcus pneumoniae, methicillin-susceptible and methicillin-resistant Staphylococcus aureus, and coagulase-neg. staphylococci. DK-507k was as active as or 4-fold more active than garenoxacin and 2- to 16-fold more active than gatifloxacin and moxifloxacin against ciprofloxacin-resistant strains of S. pneumoniae, including clin. isolates and in vitro-selected mutants with known mutations. DK-507k inhibited all ciprofloxacin-resistant strains of S. pneumoniae at 1 μg/mL. A time-kill assay with S. pneumoniae showed that DK-507k was more bactericidal than gatifloxacin and moxifloxacin. The activities of DK-507k against most members of the family Enterobacteriaceae were comparable to those of ciprofloxacin and equal to or up to 32-fold higher than those of gatifloxacin, levofloxacin, moxifloxacin, and garenoxacin. DK-507k was fourfold less active than sitafloxacin and ciprofloxacin against Pseudomonas aeruginosa, while it was two to four times more potent than levofloxacin, gatifloxacin, moxifloxacin, and garenoxacin against P. aeruginosa. In vivo, i.v. treatment with DK-507k was more effective than that with gatifloxacin and moxifloxacin against systemic infections caused by S. aureus, S. pneumoniae, and P. aeruginosa in mice. In a mouse model of pneumonia due to penicillin-resistant S. pneumoniae, DK-507k administered s.c. showed dose-dependent efficacy and eliminated the bacteria from the lungs, whereas gatifloxacin and moxifloxacin had no significant efficacy. Oral

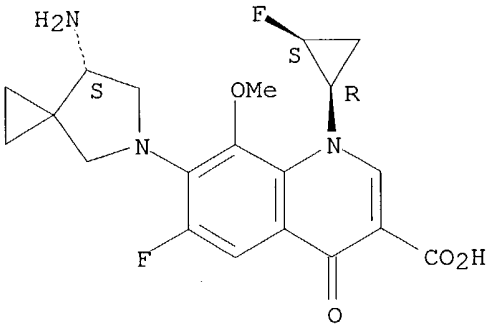
treatment with DK-507k was slightly more effective than that with ciprofloxacin in a rat model of foreign body-associated urinary tract infection caused by a P. aeruginosa isolate for which the MIC of DK-507k was fourfold higher than that of ciprofloxacin. Oral administration of DK-507k to rats achieved higher peak concns. in serum and higher concns. in cumulative urine than those achieved with ciprofloxacin. These data indicate the potential advantages of DK-507k over other quinolones for the treatment of a wide range of community-acquired infections.

IT **364069-14-7**, DK-507k
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in vitro and in vivo antibacterial activities of DK-507k, a novel fluoroquinolone)

RN 364069-14-7 CAPLUS

CN 3-Quinolinecarboxylic acid, 7-[(7S)-7-amino-5-azaspiro[2.4]hept-5-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:883789 CAPLUS

TITLE: Antibacterial susceptibility of a vancomycin-resistant Staphylococcus aureus strain isolated at the Hershey Medical Center

AUTHOR(S): Bozdogan, Buelent; Esel, Duygu; Whitener, Cynthia; Browne, Frederick A.; Appelbaum, Peter C.

CORPORATE SOURCE: Department of Pathology, Hershey Medical Center, Hershey, PA, 17033, USA

SOURCE: Journal of Antimicrobial Chemotherapy (2003), 52(5), 864-868
CODEN: JACHDX; ISSN: 0305-7453

PUBLISHER: Oxford University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Staphylococcus aureus strain HMC3 isolated at the Hershey Medical Center, was resistant to vancomycin (VRSA) through the presence of the vanA resistance gene; it also contained mecA, erm(A), erm(B), tet(K) and aac(6')-aph(2''), conferring resistance to licensed β-lactams, macrolides, tetracycline and aminoglycosides. HMC3 also had alterations in GyrA and GrlB and was resistant to available quinolones. Exptl. drugs with low MICs (<2 mg/L) for VRSA HMC3 included cephalosporins BAL9141 and RWJ-54428; glycopeptides oritavancin and dalbavancin; the lipopeptide daptomycin; the glycolipodepsipeptide ramoplanin; new fluoroquinolones WCK

771 A, WCK 1153, DK-507k and sitafloxacin; and the DNA nanobinder GS02-02. These agents were all bactericidal as were trimethoprim/sulfamethoxazole and teicoplanin (MIC 4 mg/L). Oxazolidinones linezolid and ranbezolid; the injectable streptogramin quinupristin/dalfopristin; DNA nanobinders GS2-10547 and GS02-104; peptide deformylase inhibitors NVP-PDF713 and GS02-12; tetracycline derivative tigecycline; the antifolate iclaprim; mupirocin and fusidic acid were all active in vitro but bacteriostatic.

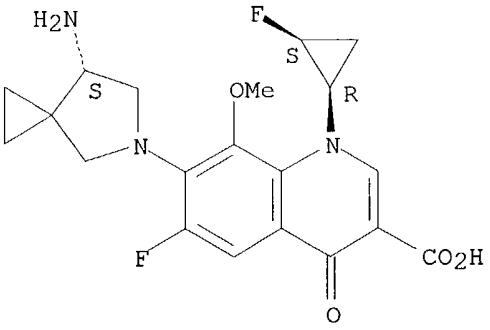
IT INDEXING IN PROGRESS

IT **364069-14-7**, DK-507k
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antibacterial susceptibility of a vancomycin-resistant Staphylococcus aureus strain isolated at the Hershey Medical Center)

RN 364069-14-7 CAPLUS

CN 3-Quinolinecarboxylic acid, 7-[(7S)-7-amino-5-azaspiro[2.4]hept-5-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:737748 CAPLUS
DOCUMENT NUMBER: 139:261175
TITLE: Preparation of quinolonecarboxylic acid derivative as antibacterial agent
INVENTOR(S): Shimizu, Sadahiro; Tani, Yuichiro; Akiba, Toshifumi
PATENT ASSIGNEE(S): Daiichi Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003076428	A1	20030918	WO 2002-JP2181	20020308

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: WO 2002-JP2181 20020308

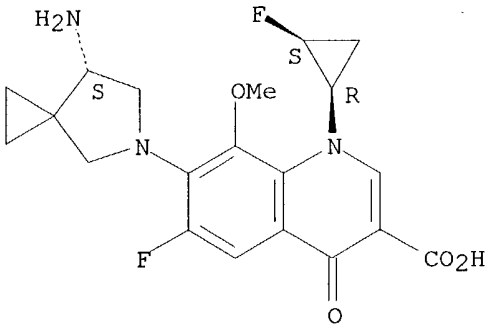
AB (-)-7-[(7S)-Amino-5-azaspiro[2.4]heptan-5-yl]-6-fluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid monohydrochloride 2.5-hydrate (I) is claimed. Also claimed is (-)-7-[(7S)-amino-5-azaspiro[2.4]heptan-5-yl]-6-fluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid monohydrochloride monohydrate (II). I and II are prepared by crystallization of (-)-7-[(7S)-amino-5-azaspiro[2.4]heptan-5-yl]-6-fluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid from a solvent containing HCl and water. I and II are antibacterial agents (no data) and show excellent stability to light and humidity.

IT **364069-13-6P 600708-59-6P**
RL: PAC (Pharmacological activity); PRP (Properties); PUR (Purification or recovery); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of quinolonecarboxylic acid derivative as antibacterial agent)

RN 364069-13-6 CAPLUS

CN 3-Quinolinecarboxylic acid, 7-[(7S)-7-amino-5-azaspiro[2.4]hept-5-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxo-, monohydrochloride, monohydrate (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



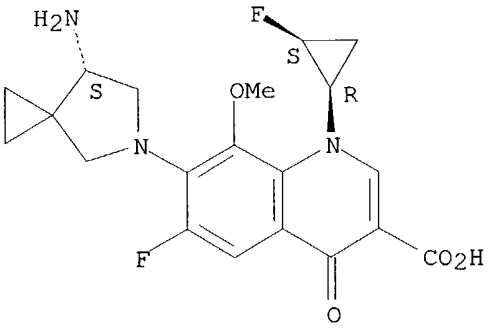
● HCl

● H_2O

RN 600708-59-6 CAPLUS

CN 3-Quinolinecarboxylic acid, 7-[(7S)-7-amino-5-azaspiro[2.4]hept-5-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxo-, monohydrochloride, hydrate (4:5) (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

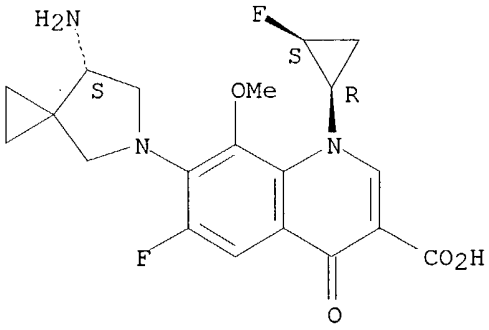


● HCl

● 5/4 H_2O

IT **364069-14-7P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of quinolonecarboxylic acid derivative as antibacterial agent)
RN 364069-14-7 CAPLUS
CN 3-Quinolinecarboxylic acid, 7-[(7S)-7-amino-5-azaspiro[2.4]hept-5-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



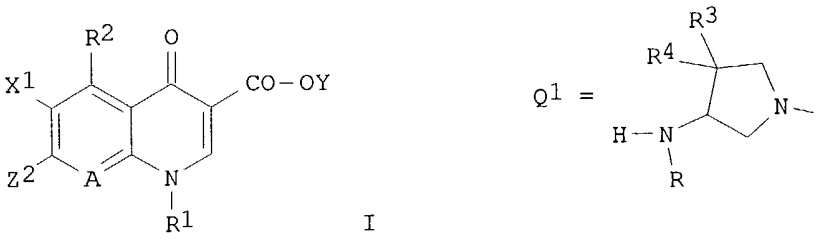
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:255404 CAPLUS
DOCUMENT NUMBER: 138:287534
TITLE: Process for preparing quinolonecarboxylic acid derivatives
INVENTOR(S): Ota, Naoki; Shirono, Toshiaki; Akiba, Toshifumi
PATENT ASSIGNEE(S): Daiichi Seiyaku Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 15 pp.
CODEN: JKXXAF

DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2003096075	A2	20030403	JP 2001-294163	20010926

PRIORITY APPLN. INFO.: JP 2001-294163 20010926
OTHER SOURCE(S): MARPAT 138:287534
GI



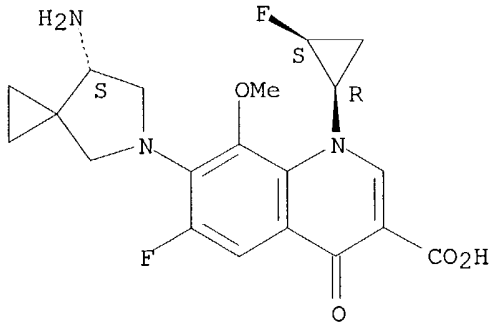
I

AB The title compds. I [X1 = H, halo; R1 = (un)substituted cycloalkyl, etc.; R2 = H, amino, etc.; A = N, etc.; Z2 = Q1, etc; R = H ; R3, R4 = H, halo, etc.] are prepared by hydrogenation of I [X1, R1 - R4, A, Z2 = as defined above; R = (un)substituted aralkyl, etc.] in an aqueous solution in the presence of an acid or base (for increasing solubility). I are useful as antibacterial agents (no data). 7-[(7S)-7-Amino-5-azaspiro[2.4]hept-5-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-8-methoxy-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid was prepared in 92% yield by the title process.

IT **364069-14-7P**
RL: IMF (Industrial manufacture); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(process for preparing aminoazaspiroheptylquinolonecarboxylic acid derivs. by hydrogenation of phenylethyl- or benzyloxycarbonylaminoazaspirohepty lquinolonecarboxylic acid derivs. in presence of acid or base)

RN 364069-14-7 CAPLUS
CN 3-Quinolinecarboxylic acid, 7-[(7S)-7-amino-5-azaspiro[2.4]hept-5-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L4 ANSWER 6 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:686503 CAPLUS
DOCUMENT NUMBER: 137:216936
TITLE: Quinolonecarboxylic acid derivatives for safe bactericides having light and moisture stability
INVENTOR(S): Shimizu, Sadahiro; Tani, Yuichiro; Akiba, Toshifumi
PATENT ASSIGNEE(S): Daiichi Seiyaku Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 11 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

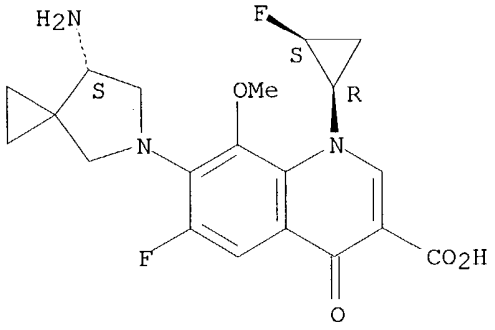
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2002255962	A2	20020911	JP 2001-50382	20010226

PRIORITY APPLN. INFO.: JP 2001-50382 20010226

AB (-)-7- {(7S)-7-amino-5-azaspiro[2.4]heptane-5-yl}-6-fluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid (I)·1HCl·2.5H2O and I·1HCl·H2O are prepared
Thus, I was prepared, suspended (3.872 g, 0.5H2O) in 23 mL iso-PrOH, dissolved in 13.4 mL water and 2.1 mL 5N HCl, mixed with 0.39 g activated carbon for 20 min, filtered, and washed with iso-PrOH, and the filtrate was crystallized to give 2.449 g I·1HCl·2.5H2O.

IT **364069-15-8P**
RL: BUU (Biological use, unclassified); IMF (Industrial manufacture); BIOL (Biological study); PREP (Preparation); USES (Uses)
(quinolonecarboxylic acid derivs. for safe and stable bactericides)
RN 364069-15-8 CAPLUS
CN 3-Quinolinecarboxylic acid, 7-[(7S)-7-amino-5-azaspiro[2.4]hept-5-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxo-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

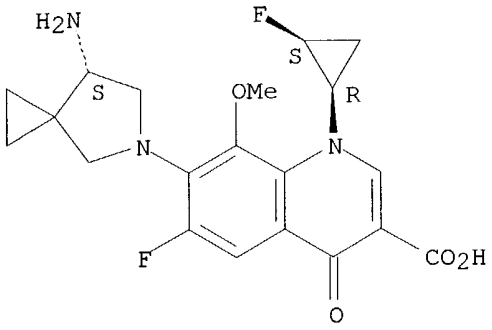


● HCl

IT **364069-14-7P**
RL: IMF (Industrial manufacture); RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)
(quinolonecarboxylic acid derivs. for safe and stable bactericides)
RN 364069-14-7 CAPLUS
CN 3-Quinolinecarboxylic acid, 7-[(7S)-7-amino-5-azaspiro[2.4]hept-5-yl]-6-

fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L4 ANSWER 7 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:533192 CAPLUS
DOCUMENT NUMBER: 137:93736
TITLE: Preparation of quinolonecarboxylic acid derivative as bactericide and its intermediates
INVENTOR(S): Shimizu, Sadahiro; Makino, Toru; Kino, Toshiaki; Nagasawa, Hiroshi; Ota, Naoki; Akiba, Toshifumi
PATENT ASSIGNEE(S): Daiichi Seiyaku Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 16 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2002201191	A2	20020716	JP 2001-296115	20010927

PRIORITY APPLN. INFO.: JP 2000-297171 A 20000928
OTHER SOURCE(S): CASREACT 137:93736; MARPAT 137:93736
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

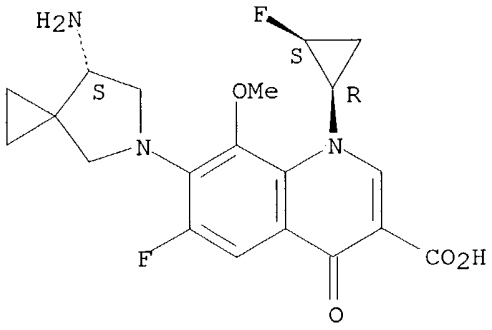
AB Title derivative I (R1 = R2 = H) is prepared by treatment of 6,7-difluoroquinolonecarboxylic acids II (R1 = H, BX2; X = F, C1-6 alkoxy, C2-7 alkylcarbonyloxy) with 7-(S)-amino-5-azaspiroheptanes III (R2 = H, alkoxycarbonyl, aralkyloxycarbonyl, acyl, aralkyl, etc.; when R1 = BF2, then R2 ≠ H, tert-butoxycarbonyl), followed by optional deboronation and/or removal of R2. Thus, 7-(S)-amino-5-azaspiro[2.4]heptane 2HCl salt was treated with Et3N at 30° for 18 h in N,N-dimethylacetamide, then treated with II (R1 = H) at 60° for 24 h to give 60% I (R1 = R2 = H).

IT **364069-14-7P**
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of quinolonecarboxylic acid derivative as bactericide)

RN 364069-14-7 CAPLUS

CN 3-Quinolinecarboxylic acid, 7-[(7S)-7-amino-5-azaspiro[2.4]hept-5-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L4 ANSWER 8 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:408080 CAPLUS
DOCUMENT NUMBER: 137:319954
TITLE: In vitro photochemical clastogenicity of quinolone antibacterial agents studied by a chromosomal aberration test with light irradiation
AUTHOR(S): Itoh, Satoru; Nakayama, Shiho; Shimada, Hiroyasu
CORPORATE SOURCE: Drug Safety Research Laboratory, Daiichi Pharmaceutical Co. Ltd., Tokyo, 134-8630, Japan
SOURCE: Mutation Research (2002), 517(1-2), 113-121
CODEN: MUREAV; ISSN: 0027-5107
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

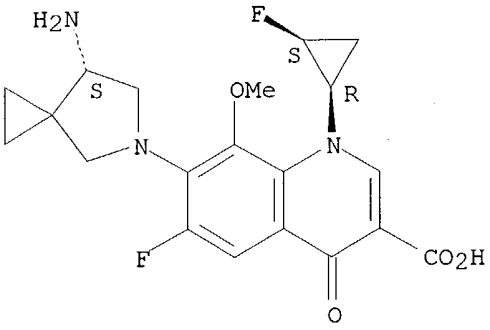
AB The photochem. clastogenic potential of 12 quinolone antibacterial agents with or without light irradiation was assessed by an in vitro chromosomal aberration test using cultured CHL cells. Exposure to all test compds., except for DK-507k, increased the incidence of cells with structural aberrations excluding gap (TA) following light irradiation Test compds. used in the present study under light irradiation were divided into three groups based on their ED50 values, doses inducing chromosomal aberrations in 50% of cells. The first group with ED50 values below 30 μg/mL includes sparfloxacin (SPFX), clinafloxacin (CLFX), gemifloxacin (GMFX), lomefloxacin (LFLX), sitafloxacin (STFX), grepafloxacin (GPFX) and fleroxacin (FLRX); the second group with ED50 values of 100 μg/mL, enoxacin (ENX) and levofloxacin (LVFX); the third group with little or no potency, moxifloxacin (MFLX), trovafloxacin (TVFX) and DK-507k. The photochem. clastogenicity of these compds. correlates well with their reported in vivo phototoxic potentials. In the chemical structure and clastogenicity relationships, substitution of a methoxy group at the C-8 position in the quinolone nucleus was confirmed to reduce not only photochem. clastogenicity, but also the clastogenic potential of quinolone antibacterial agents.

IT **364069-14-7**, DK 507k
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(photochem. clastogenicity of quinolone antibacterial agents: chromosomal aberration test with light irradiation)

RN 364069-14-7 CAPLUS
CN 3-Quinolinecarboxylic acid, 7-[(7S)-7-amino-5-azaspiro[2.4]hept-5-yl]-6-

fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:730731 CAPLUS
DOCUMENT NUMBER: 135:288695
TITLE: Preparation of antibacterial fluoroquinolonecarboxylic acid derivative
INVENTOR(S): Takemura, Makoto; Takahashi, Hisashi; Kawakami, Katsuhiro; Itoh, Masao; Suzuki, Tetsuya; Ohtani, Tsuyoshi; Sekiguchi, Masayasu; Miyauchi, Rie; Hayakawa, Isao
PATENT ASSIGNEE(S): Daiichi Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001072738	A1	20011004	WO 2001-JP2761	20010330
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 2001044671	A5	20011008	AU 2001-44671	20010330
JP 2003073275	A2	20030312	JP 2002-9952	20010330
EP 1298131	A1	20030402	EP 2001-917706	20010330
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2001011248	A	20030708	BR 2001-11248	20010330
NO 2002005542	A	20021126	NO 2002-5542	20021119
US 2003187008	A1	20031002	US 2003-275972	20030331

PRIORITY APPLN. INFO.: JP 2000-97690 A 20000331
JP 2000-271231 A 20000907

JP 2001-570649 A3 20010330
WO 2001-JP2761 W 20010330

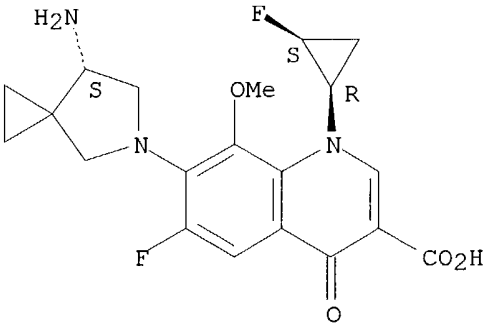
AB Claimed is (-)-7-[(7S)-7-amino-5-azaspiro[2.4]heptan-5-yl]-6-fluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid monohydrochloride monohydrate (I). I was prepared and showed MIC values of ≤ 0.003 μg/mL and 0.05 μg/mL against E. coli NIHJ and P. aeruginosa 32121, resp. I is highly stable to light and humidity.

IT **364069-13-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of antibacterial fluoroquinolonecarboxylic acid derivative)

RN 364069-13-6 CAPLUS

CN 3-Quinolinecarboxylic acid, 7-[(7S)-7-amino-5-azaspiro[2.4]hept-5-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxo-, monohydrochloride, monohydrate (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



● HCl

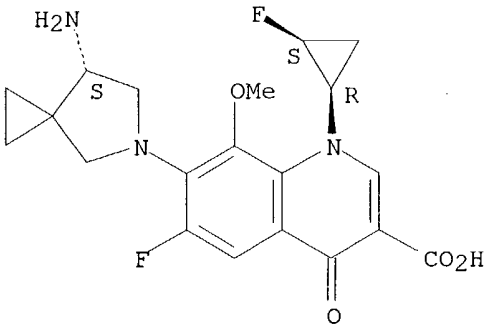
● H_2O

IT **364069-14-7P 364069-15-8P 364069-16-9P**
364069-17-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of antibacterial fluoroquinolonecarboxylic acid derivative)

RN 364069-14-7 CAPLUS

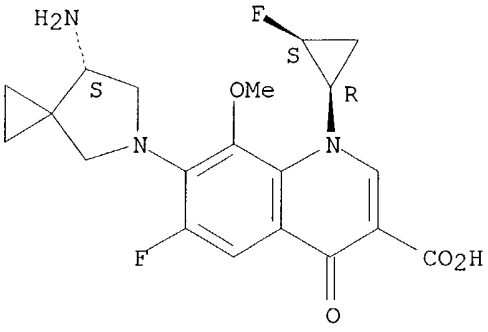
CN 3-Quinolinecarboxylic acid, 7-[(7S)-7-amino-5-azaspiro[2.4]hept-5-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 364069-15-8 CAPLUS
CN 3-Quinolinecarboxylic acid, 7-[(7S)-7-amino-5-azaspiro[2.4]hept-5-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxo-, monohydrochloride (9CI) (CA INDEX NAME)

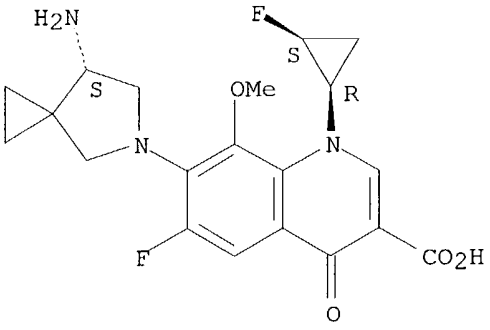
Absolute stereochemistry. Rotation (-).



● HCl

RN 364069-16-9 CAPLUS
CN 3-Quinolinecarboxylic acid, 7-[(7S)-7-amino-5-azaspiro[2.4]hept-5-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxo-, monohydrate (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



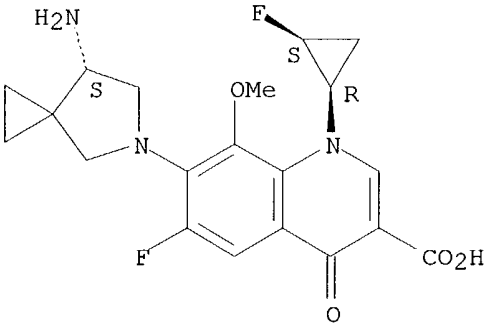
● H_2O

RN 364069-17-0 CAPLUS
CN 3-Quinolinecarboxylic acid, 7-[(7S)-7-amino-5-azaspiro[2.4]hept-5-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxo-, monomethanesulfonate (9CI) (CA INDEX NAME)

CM 1

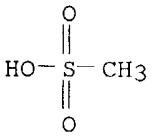
CRN 364069-14-7
CMF C20 H21 F2 N3 O4

Absolute stereochemistry. Rotation (-).



CM 2

CRN 75-75-2
CMF C H4 O3 S

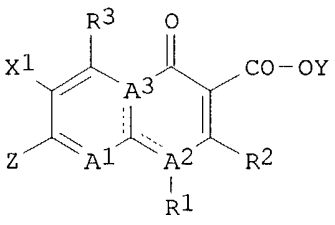


REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 10 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:597964 CAPLUS
DOCUMENT NUMBER: 135:180773
TITLE: Preparation of oxoquinolinecarboxylic acid, oxonaphthyridinecarboxylic acid, and pyridobenzoxazinecarboxylic acid derivatives as antibacterial agents
INVENTOR(S): Takemura, Makoto; Takahashi, Hisashi; Kawakami, Katsuhiro; Namba, Kenji; Tanaka, Mayumi; Miyauchi, Rie
PATENT ASSIGNEE(S): Daiichi Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 104 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001058876	A1	20010816	WO 2001-JP861	20010207
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 2001032238	A5	20010820	AU 2001-32238	20010207
EP 1262477	A1	20021204	EP 2001-904335	20010207
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2003119848	A1	20030626	US 2002-203199	20020807
NO 2002003764	A	20021009	NO 2002-3764	20020808

PRIORITY APPLN. INFO.: JP 2000-38099 A 20000209
WO 2001-JP861 W 20010207
OTHER SOURCE(S): MARPAT 135:180773
GI



I

AB The title compds. I [R1 = alkyl, etc.; R2 = H, alkylthio; further details on R1 and R2 are given; R3 = H, alkoxy, etc.; A1 = N, etc.; A2, A3 = N, C; further details on A1, A2, A3 are given; X1 = halo, etc.; Y = H, Ph, etc.; Z = heterocyclic substituent; further details on said heterocyclic substituent are given] are prepared I show excellent antibacterial activity (against M. tuberculosis and atypical acid-fast bacteria), favorable

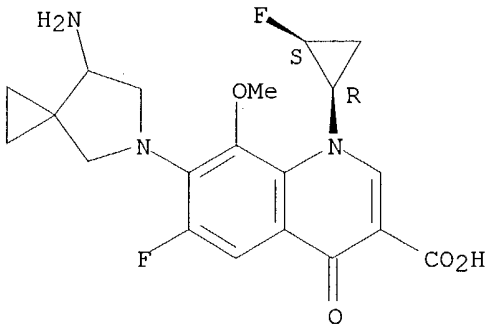
kinetics in vivo and high safety. Several compds. of this invention in vitro show MICs of 0.78 μg/mL to 3.13 μg/mL against rifampicin-resistant M. tuberculosis, vs. MIC of 25 μg/mL shown by ofloxacin. Formulations are given.

IT **354812-43-4P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of oxoquinolinecarboxylic acid, oxonaphthyridinecarboxylic acid, and pyridobenzoxazinecarboxylic acid derivs. as antibacterial agents)

RN 354812-43-4 CAPLUS

CN 3-Quinolinecarboxylic acid, 7-(7-amino-5-azaspiro[2.4]hept-5-yl)-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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FILE 'REGISTRY' ENTERED AT 17:58:52 ON 29 JUN 2004
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L2 0 S L1
L3 7 S L1 FULL

FILE 'CAPLUS' ENTERED AT 17:59:24 ON 29 JUN 2004
L4 10 S L3

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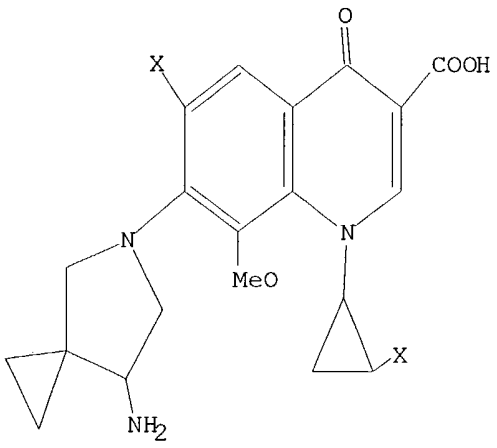
L1 HAS NO ANSWERS
L1 STR



Structure attributes must be viewed using STN Express query preparation.

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